

Evaluation of Maximum to Specific Power Consumption Ratio in Shaking Bioreactors

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Among others, the maximum power consumption in a fermentation broth is one of the most decisive engineering parameters to characterize culture conditions and to scale-up bioprocesses, especially with filamentous microorganisms. Based on the fact that maximum drop diameter in coalescence inhibited two-phase dispersing processes is solely dependent on maximum power consumption, no matter which dispersing machine is used, drop sizes were measured in shaking bioreactors and the ratios between maximum and specific power consumption were calculated. In agreement with two different simplifying theoretical considerations relatively small ratios are obtained. It is concluded that the power consumption in shaking bioreactors is much more evenly distributed than in stirred tank fermentors. As the specific power consumptions in both types of bioreactors are of the same order of magnitude, shaking bioreactors create much lower levels of hydromechanical stress to microorganisms and dispersed phases.

Introduction

Shaking flasks with a total nominal volume of 50 ml to 5 l are widely used for screening projects or for small scale production of valuable products in bioindustry. The flasks are filled with liquid culture medium with a volume of about 1/50 to 1/5 of the nominal flask volume, and are most frequently operated on orbital shaking machines at specific shaking frequencies. Through driving centrifugal acceleration, the liquid circulates inside the flasks, resulting in characteristic degrees of liquid mixing and mass transfer, for example. The liquid distribution (for an example, please refer to Büchs *et al.*, 2000b) and the flow regime inside the flasks is dependent on the different operating parameters. Usually turbulent conditions are predominant. In some cases, when small flasks, elevated viscosity and/or low shaking frequencies are used, the transition regime is reached (Büchs *et al.*, 2000b).

The major advantage of shaking flasks is their ease of handling. A large number of experiments can be carried out simultaneously with a minimum material expense and practically no supervision. In larger companies working in the field of biotechnology several

10,000 up to several 100,000 experiments are carried out using shaking flasks annually. Since very decisive selecting and directing is undertaken using shaking flasks, it must be ensured that this does not take place under unsuitable, non-consistent experimental conditions. Screening under unknown limitations can lead to failure or at least to a development in completely unwanted directions. An accurate definition of the factors influencing the performance of shaking bioreactors is therefore indispensable.

Nowadays, the design of bioprocesses in stirred tank fermentors with a standard geometry is no longer a big problem. In contrast, shaking flasks in which the major part of biotechnological development takes place are only insufficiently described. One of the important parameters in fermentation of aerobic microbes in shaking bioreactors and stirred tank fermentors is the average or specific power consumption (per unit volume) $(P/V)_0$. We have developed a new method, which enables accurate determination of the specific power consumption in a shaking flask down to a nominal size of 100 ml (Büchs *et al.*, 2000a). From these measurements it is noticeable that in shaking flasks relatively high levels of the specific power consumption are achieved, which are at least of the same order of magnitude as the usual values for stirred tank fermentors.

Some bioprocesses, however, are predominantly controlled by the level of hydromechanical stress. These are processes with plant or animal cells or microorganisms showing filamentous morphology. Oth-

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ers are processes containing a second liquid phase of an organic carbon source like plant oil, alkanes, or water insoluble chemicals introduced for bioconversion. In all these cases, the distribution of the power consumption or at least its maximum value $(P/V)_{\max}$ has to be known to sufficiently characterise the bioprocess. The knowledge of the ratio of the maximum to specific power consumption $(P/V)_{\max}/(P/V)_{\emptyset}$ will also help to estimate the mixing conditions in shaking bioreactors.

1. Concept of Measurement

Bauer (1985) and Davies (1987) have independently shown that the drop diameter in a coalescence inhibited two-phase liquid system under conditions of free isotropic turbulence is dependent on the maximum value of the power consumption or energy dissipation rate, respectively, no matter which dispersing machine is used. These authors could show that a universal correlation of $d_{\max} = f((P/V)_{\max})$ exists for stirred tank reactors, static mixers, colloid mills, liquid whistles, valve homogenizers and ultrasonics, demonstrating the general validity of this finding.

Based on this we attempted to:

- 1) develop a stable and well defined coalescence inhibited two-phase liquid system with balanced density, suitable for dispersing and measuring of drop diameters,
- 2) measure the specific power consumption $(P/V)_{\emptyset}$ in shaking bioreactors for different operating conditions,
- 3) measure drop size distributions for different operating conditions in shaking bioreactors and stirred tank fermentors with a Fraunhofer laser diffraction spectrometer and convert this information into the corresponding maximum stable drop diameters d_{\max} ,
- 4) calibrate the function $d_{\max} = f((P/V)_{\max})$ in a well defined stirred tank fermentor, for which the maximum power consumption $(P/V)_{\max}$ for different operating conditions is known,
- 5) calculate the maximum power consumption $(P/V)_{\max}$ in shaking bioreactors with the aid of this calibration function from the corresponding maximum stable drop diameters d_{\max} , measured for different operating conditions. As a result the $(P/V)_{\max}/(P/V)_{\emptyset}$ ratios can be calculated.

A somehow similar approach has already been applied by Takebe *et al.* (1971). They evaluated drop sizes as indicators for what they termed "agitation intensity." The authors scaled-up fermentations with a filamentous fungi from shaking flasks to stirred tank fermentors by keeping the "agitation intensity" constant. No attempts were made, however, to derive information about maximum power consumption from the drop sizes.

2. Material and Methods

2.1 Bioreactors

Narrow necked 100-, 250-, 500- and 1000-ml Erlenmeyer flasks without baffles according to the German standard DIN 12380 were used. Additionally a 300-ml baffled Erlenmeyer flask from B. Braun Biotech (product number: 886 100/5, Melsungen, Germany), which contained three machine-made indentations, separated from each other by 120°, 1.4 cm deep and 6.5 cm high was included in our measurement program. Hydrophobic glass walls were produced by boiling the shaking flasks in 10% nitric acid, rinsing with water, and shaking a solution of 5% dichlorodimethylsilane (Sigma, Germany) in toluene in the shaking flasks for 10 minutes and drying the flasks for 24 hours at ambient temperature. All experiments with Erlenmeyer flasks were performed on orbital shaking machines with shaking diameters of 2.5 cm (Certomat R, B. Braun Biotech, Melsungen, Germany) or of 5 cm (TR-150, Infors, Bottmingen, Switzerland). A fully baffled 14-l stirred tank fermentor (SG 14, Chemap, Switzerland) with an inner diameter and a filling height of 0.22 m, resulting in a filling volume of 8.4 l was used. The vessel was equipped with a standard Rushton turbine of 0.07-m diameter mounted at half the filling height. The stirrer was driven by an electric drive, equipped with a torque meter (Ikavic MR D1, Jahnke and Kunkel GmbH, Staufen/Breisgau, Germany) with a sensitivity of 0–1 N m. The stirring speed and torque meter signals were connected to a data acquisition system. For this experimental set-up, a power number of $c_p = 3.95$ was evaluated. The stirring speed could only be varied between 160 and 500 1/min. The lower boundary must be exceeded to fulfil Eq. (6) (see below) as a prerequisite for free isotropic turbulence. The upper boundary represents the stirring speed above which air is introduced into the liquid by turbulent vortexes.

2.2 Model liquid

To ensure that the different levels of centrifugal acceleration in shaking bioreactors and stirred tank fermentors do not influence the level of drop dispersion, an aqueous/organic two-phase liquid system with balanced density was developed. The organic dispersed phase consisted of a mixture of four volumetric parts toluene and one part carbon tetrachloride. This mixture had the same density of about 1 kg/l as the aqueous phase. It is shown, though, that for small deviations from the density balanced situation (dispersed phase densities of 0.93 and 1.2 kg/l respectively) the drop diameters do not differ significantly. The relative amount of the dispersed phase was 3%. As the pH value of the aqueous phase may influence the surface charge of the droplets and therefore the dispersion intensity, the aqueous solution was buffered with 40 mM Tris buffer (analytical grade, E. Merck, Darmstadt, Germany). The pH was adjusted to a value of 7.5 by adding concentrated hydrochloric acid. To obtain a well

defined coalescence inhibited liquid system 0.5% (w/v) of a fast surfactant (LEO 30: lauryl ethylene oxide with 30 repeating ethylene oxide units, BASF AG, Ludwigshafen, Germany) was added to the continuous aqueous phase. Some experiments were also conducted with 0.05% (w/v) LEO 30. The kinematic viscosity of the aqueous phase was $0.92 \times 10^{-6} \text{ m}^2/\text{s}$. The surface tension between aqueous and organic phase was 0.0047 N/m.

2.3 Measuring devices and data evaluation

The device for measuring the specific power consumption in shaking flasks is described elsewhere (Büchs *et al.*, 2000a). The drop size distributions were measured with a Fraunhofer laser diffraction spectrometer (Particle Sizer 2600, Müttek-Malvern, Herrenberg, Germany) with a beam length of 12 mm and a lens with a focal length of 300 mm (drop size measurement range: 5.8–564 μm). The measuring cell was filled with aqueous phase and the measuring background was evaluated. After the shaking bioreactors or the stirred tank fermentor were operated for at least 20 minutes to ensure complete dispersion, samples were taken with a pipette. A specific amount of sample liquid was added to the measuring cell in order to obtain a suitable concentration (obscuration of 0.2–0.4), according to the instructions of the manufacturer of the Particle Sizer. At least 1200 drops were evaluated for one drop size distribution (lasting about 9 seconds). It was shown by comparative measurements that the dispersions were absolutely stable for at least 24 hours. The cumulative volume frequency was calculated from:

$$H_3(d_j) = \frac{\sum_{i=1}^j V_i}{\sum_{i=1}^n V_i} \quad (1)$$

The measured drop size distributions always show a bimodal pattern with a high maximum at large drop sizes and a low maximum at small drop sizes. **Figure 1** shows an example. The drop size distribution curves for dispersions from shaking bioreactors and stirred tank fermentors have a very similar shape in all cases, indicating a similar dispersion mechanism in both types of bioreactors. For our purposes, only the high maximum portion of the drop size distribution is evaluated. As this part of the drop size distribution shows a skewed or log-normal distribution, the following equation is used to describe the volume frequency (Bauer, 1985):

$$h_3(d) = \frac{1}{\sigma \cdot \sqrt{2} \cdot \pi} \cdot e^{-\frac{\log\left(\frac{d}{d_{\text{Mod}}}\right)^2}{2 \cdot \sigma^2}} \quad (2)$$

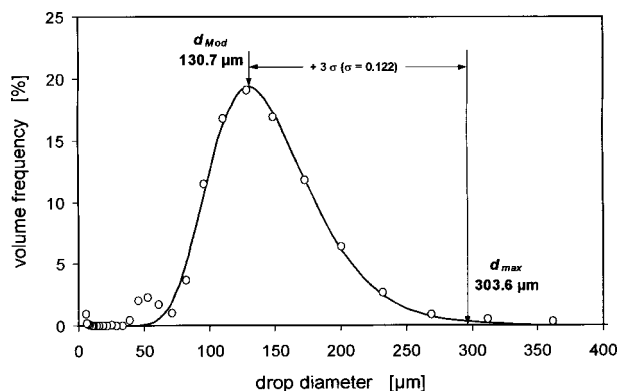


Fig. 1 Example of volume frequency of drop dispersion generated in 250-ml shaking flask with 25-ml filling volume at shaking frequency of 300 1/min on shaking machine with shaking diameter of 2.5 cm. Log-normal distribution (Eq. (2)) was fitted through measuring points specifying parameter d_{Mod} and maximum stable drop diameter d_{max}

d_{Mod} represents the drop size at the turning point of the cumulative volume frequency (H_3) or at the maximum of the volume frequency (h_3). As illustrated in Fig. 1, the maximum stable drop diameter is defined as the drop diameter at the 99.85% level of the cumulative volume frequency (Schubert *et al.*, 1977):

$$d_{\text{max}} = 10^{(\log d_{\text{Mod}} + 3 \cdot \sigma)} \quad (3)$$

3. Theory of Power Consumption

Several literature sources deal with the ratio of the maximum to specific power consumption $(P/V)_{\text{max}} / (P/V)_{\emptyset}$ in stirred tanks (Cutter, 1966; Okamoto *et al.*, 1981; Laufhütte and Mersmann, 1985; Wu and Patterson, 1989; Stahl Wernersson and Trägardh, 1998). The published ratios for standard Rushton turbines vary between about 30 and 200. In this work the $(P/V)_{\text{max}} / (P/V)_{\emptyset}$ ratios are calculated according to the relation (Liepe *et al.*, 1988):

$$\frac{(P/V)_{\text{max}}}{(P/V)_{\emptyset}} = \frac{c_D \cdot \pi^3 \cdot d_2}{c_P \cdot h_1} \cdot \frac{V}{d_2^3} \quad (4)$$

For our experimental set-up with $c_D = 0.1$ (according to Liepe *et al.*, 1988), $d_2 = 0.07 \text{ m}$, $V = 8.4 \text{ l}$, $c_P = 3.95$, $h_1 = 0.0136 \text{ m}$ a ratio of $(P/V)_{\text{max}} / (P/V)_{\emptyset} = 100$ results.

A universal equation for the calculation of the maximum power consumption is given by (Liepe *et al.*, 1988):

$$(P/V)_{\text{max}} = \frac{c_D \cdot (\pi \cdot n \cdot d_2)^3}{h_1} \cdot \rho_c \quad (5)$$

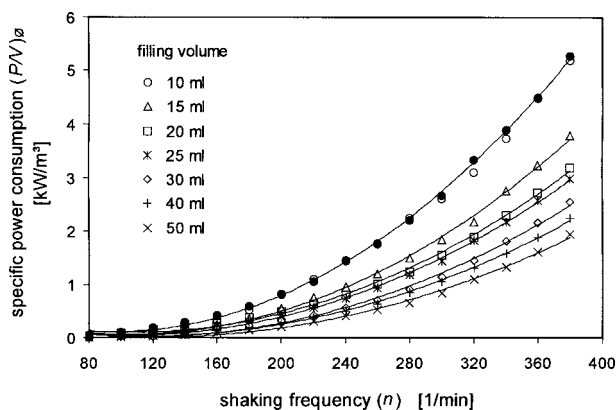


Fig. 2 Specific power consumption in 250-ml Erlenmeyer flasks at different shaking frequencies and filling volumes, 2.5-cm shaking diameter. Filled and open symbols in case of 10 ml filling volume indicate reproduced measurement series, taken after 3 months

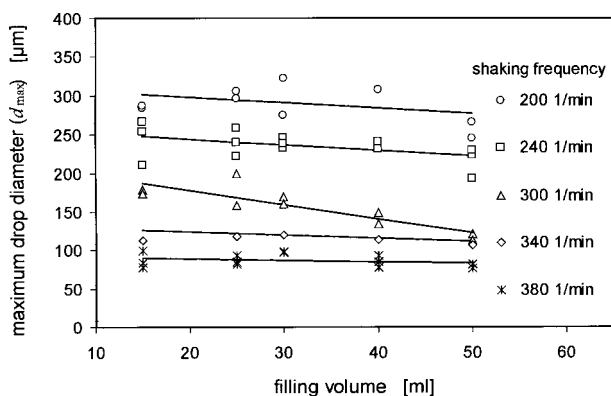


Fig. 3 Maximum drop diameters in unbauffed 250-ml Erlenmeyer flasks with different filling volumes and shaking frequencies, 2.5-cm shaking diameter, 0.5% (w/v) LEO 30

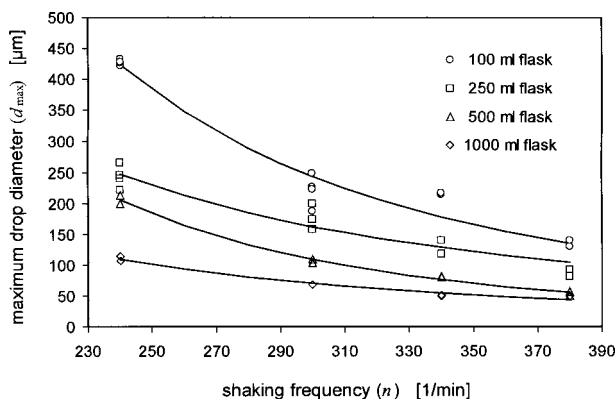


Fig. 4 Maximum drop diameters in different unbauffed Erlenmeyer flask sizes with filling volume of one-tenth of nominal volume, and 2.5-cm shaking diameter

The validity of the assumption of free isotropic turbulence can be determined from (Liepe *et al.*, 1988):

$$\frac{\Lambda_f}{l_D} > 150 \dots 200 \quad (6)$$

with

$$\Lambda_f \approx 0.4 \cdot h_1 \quad (7)$$

$$l_D = 4 \sqrt{\frac{v^3}{(P/V)_{\max} / \rho_c}} \quad (8)$$

Where Λ_f is the macro-scale of turbulence and l_D is the Kolmogoroff or micro-scale of turbulence.

The thickness of the turbulent liquid boundary layer around a rotating disk is given by (Schlichting, 1982):

$$\delta_D = 0.526 \cdot r \cdot \sqrt[5]{\frac{v}{r^2 \cdot 2 \cdot \pi \cdot n}} \quad (9)$$

4. Results and Discussion

To examine the specific power consumption in 250 ml Erlenmeyer flasks, measurements were performed at different filling volumes and shaking frequencies. **Figure 2** shows the results of the examinations. It is noticeable that in shaking flasks a relatively high power consumption is obtained, which is at least of the same order of magnitude as the usual values in stirred tanks. The power consumption increases with higher shaking frequencies, as expected. With increasing filling volume the power consumption decreases since the friction surface between glass wall and liquid does not rise directly proportional with respect to the filling volume.

Figure 3 shows the maximum drop diameters in unbauffed 250-ml shaking flasks at various filling volumes and shaking frequencies. The drop diameters decrease with increasing shaking frequency. The filling volume obviously has no significant influence on the dispersion intensity. Experiments with a surfactant (LEO 30) concentration of 0.05% (w/v) (results not shown) revealed exactly the same tendency as Fig. 3. The somewhat larger slope of the curve representing a shaking frequency of 300 1/min in Fig. 3 is probably due to measuring inaccuracies. For 300 1/min with a surfactant concentration of 0.05% (w/v) no decreasing tendency is observed. The drop break-up occurs in the boundary layer near the glass wall of the flask. The speed of the liquid relative to the glass wall is independent of the filling volume. Consequently, the filling volume has no influence on the drop dispersion. In

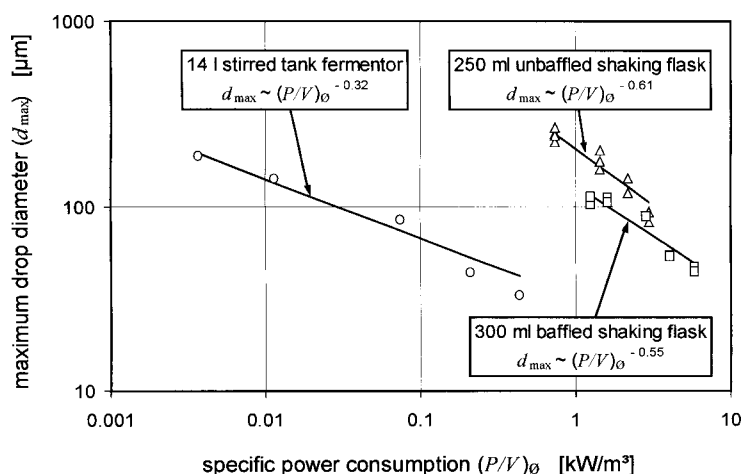


Fig. 5 Maximum drop diameters in different types of bioreactors as function of specific power consumption. Filling volume is always one-tenth of nominal volume. Shaking diameter is 2.5 cm

Fig. 4 the maximum drop diameter is compared for different sizes of unbaffled flasks. At the same shaking frequency, the drops become smaller in larger flasks. The reason for this is again assumed to be the higher relative speed between liquid and flask wall at larger flask diameters. This also agrees with the fact that at equal shaking frequencies and relative filling volume ratios the specific power consumption in larger flasks is higher than in smaller flasks (Büchs *et al.*, 2000a). For unbaffled 100-, 250-, 500- and 1000-ml Erlenmeyer flasks, no differences in maximum drop diameter are found whether the dispersion is produced on a shaking machine with 2.5 or 5 cm shaking diameter (results not shown). This corresponds to the finding that the specific power consumption in these flasks does not differ significantly at both shaking diameters mentioned (Büchs *et al.*, 2000a). Also no differences in maximum drop diameter (results not shown) nor specific power consumption (Büchs *et al.*, 2000a) are observed for flasks with hydrophilic and hydrophobic surface properties of the inner glass walls. The maximum drop diameters for the baffled 300 ml flask (not shown in Fig. 4) lie in a region close to the results of the unbaffled 1000-ml flask. This indicates that baffling increases the dispersion intensity relative to unbaffled flasks.

In **Fig. 5**, the maximum drop diameters obtained from two types of shaking flasks and from the 14-l stirred tank fermentor are depicted as a function of the specific power consumption. In the double logarithmic plot, linear correlations are observed. In the case of the stirred tank fermentor, an exponent of -0.32 results. This value agrees very well with the value of -0.33 given by Liepe *et al.* (1988) for the dispersing conditions used in this examination. The exponents for the shaking flasks are -0.55 to -0.61 . The results for the other unbaffled flasks (100, 500 and 1000 ml) are positioned between the results of the unbaffled 250-

ml flask and the baffled 300-ml flask, and are not shown in Fig. 5, to preserve clearness. The comparison of the maximum stable drop diameters measured for the shaking bioreactors and for a stirred tank fermentor demonstrates that the organic liquid phase is much better dispersed in the last mentioned type of bioreactor. At equal specific power consumption, the drops in the shaking bioreactors are about four to six times larger than in a stirred tank fermentor.

Since the ratio $(P/V)_{\max}/(P/V)_0$ is known for our stirred tank fermentor (≈ 100) from Eq. (4), it is now possible to establish a calibration function $d_{\max} = f((P/V)_{\max})$ for our specific two-phase liquid system. According to our concept, the maximum power consumption in shaking flasks is derived from the measured maximum drop diameters with this calibration function. We then evaluate the ratios between the maximum and specific power consumption in shaking bioreactors by using the measured specific power consumption. **Figure 6** shows the results of these calculations. The $(P/V)_{\max}/(P/V)_0$ ratios obtained are generally very small (the ratios < 1 will be discussed below). This general finding is supported by two simplifying theoretical considerations:

The ratio $(P/V)_{\max}/(P/V)_0$ can also be regarded as the ratio between the portion of the liquid volume, into which the power is actually introduced, and the total liquid volume. In case of a stirred tank fermentor the power introducing element is the stirrer. In case of a shaking bioreactor, the wetted glass wall has to be regarded as the "stirring element." The first mentioned volume can roughly be estimated by calculating the thickness of the turbulent liquid boundary layer close to the wetted glass wall using Eq. (9). The maximum inner radius of the flasks was used for r . This boundary layer thickness is then multiplied by the contact area between rotating liquid and glass wall. This contact area can be estimated from photographs or theo-

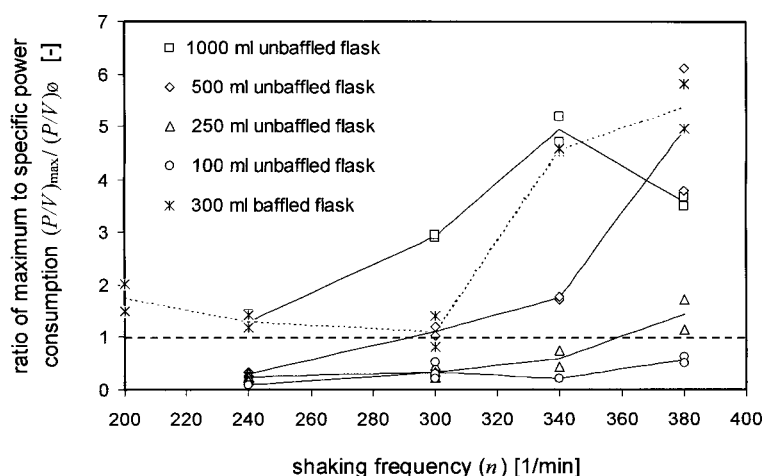


Fig. 6 Ratios between maximum and specific power consumption in different shaking bioreactors as function of shaking frequency. Filling volume is always one-tenth of nominal volume. Shaking diameter is 2.5 cm

retically calculated (Maier and Büchs, 2001). From these calculations $(P/V)_{\max}/(P/V)_0$ ratios between 1.4 and 2 result for the un baffled flasks and the operating conditions shown in Fig. 6.

Using Eq. (5), $(P/V)_{\max}$ is calculated and divided by the specific power consumption measured in shaking flasks. The maximum inner flask diameter was used for d_2 and the maximum height of the rotating liquid (from photographs or theoretical calculations, Maier and Büchs, 2001), which actually has to be regarded as the “stirrer height”, for h_1 . With $c_D = 0.1$, $(P/V)_{\max}/(P/V)_0$ ratios between 3 and 7 are obtained.

It is interesting to note that under some specific operating conditions of shaking bioreactors $(P/V)_{\max}/(P/V)_0$ ratios < 1 are also obtained in our measurements (Fig. 6). This result is physically not reasonable, of course. These conflicting findings are probably due to non-isotropic turbulent conditions in shaking bioreactors, which were the basis of our concept of measurement. According to Eq. (6) a prerequisite for isotropic turbulence is a ratio of the macro-scale (Λ_p) to the micro-scale (l_p) of turbulence of >200 . This is not always fulfilled especially in small shaking bioreactors (small h_1), questioning the applicability of our concept of measurement for these cases. But as a consequence, non fully isotropic turbulent conditions will lead to even lower levels of hydromechanical stress, which is the finally decisive parameter for a bioprocess.

Conclusion

Generally, the values of the $(P/V)_{\max}/(P/V)_0$ ratios in shaking flasks of 1 to 7, measured by evaluating drop sizes, agree reasonably well with the results of two different theoretical considerations. The ratios in shaking bioreactors are at least one order of magnitude smaller than in standard stirred tank fermentors. The only possible conclusion is that the power con-

sumption in shaking bioreactors is much more evenly distributed than in stirred tanks. These general results are not really surprising. A comparison of the relative size of the power introducing devices of the two bioreactors considered is very helpful. In case of the stirred tank fermentor a relatively small stirrer agitates in a relatively bulky tank, leading to high power consumption in the region adjacent to the stirrer and only low levels of power consumption in areas distant to the stirrer. In case of shaking bioreactors a rather large flask wall area relative to the total filling volume introduces the energy, leading to the homogeneous distribution of power consumption which we have actually found.

Our findings also correspond with the general well-established experience of microbiologists that filamentous microorganisms tend to form significantly larger pellets in shaking flasks than in stirred tank fermentors. As we have shown, this is not due to different levels of specific power consumption but a result of significantly different levels of maximum power consumption, i.e. hydromechanical stress. We regard this difference as being too large to scale-up a bioprocess from shaking bioreactors to stirred tank fermentors by using the criteria of a constant level of maximum power consumption. Takebe *et al.* (1971), neither with baffled nor with un baffled shaking flasks, were able to raise the “agitation intensity” to the optimum level of their specific process. This is a very important general conclusion for future bioprocess development.

Nomenclature

c_D	=	dissipation parameter	[—]
c_p	=	power number	[—]
d	=	drop diameter	[m]
d_2	=	stirrer diameter or maximum inner flask diameter	[m]
d_{\max}	=	maximum stable drop diameter	[m]

d_{Mod}	=	drop size at the turning point of the cumulative volume frequency H_3	[m]
H_3	=	cumulative volume frequency	[—]
h_1	=	stirrer height or maximum liquid height	[m]
h_3	=	volume frequency	[—]
l_D	=	micro-scale of turbulence	[m]
n	=	shaking frequency	[1/min]
$(P/V)_{max}$	=	maximum power consumption	[W/m ³]
$(P/V)_0$	=	specific power consumption	[W/m ³]
r	=	disk radius or inner flask radius	[m]
V	=	filling volume	[m ³]
V_i	=	drop volume	[m ³]
δ_D	=	thickness of turbulent liquid boundary layer	[m]
ν	=	kinematic viscosity	[m ² /s]
ρ_c	=	density of the continuous phase	[kg/l]
σ	=	standard deviation	[—]
Λ_f	=	macro-scale of turbulence	[m]

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